ROLE OF CHEMOTHERAPY IN MALIGNANCY

THESIS

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C E R T I F I C A T E

This is to certify that the work entitled "Role of Chemotherapy in Malignancies" which is being submitted as thesis for M.S. (general surgery) examination, 1990 of Bundelkhand University, by Dr. Govind Gopal singhal (Demonstrator, Deptt. of surgery), has been carried out under my guidance and supervision. His results and observations have been checked and verified by me from time to time.

He has put in the necessary stay in the Department of Surgery as per University rules and regulations.

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Dated : 14.9.89

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GOVIND GOPAL SINGHAL

C O N T E N T S

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INTRODUCTION

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There is no term in the entire lexicon of medicine that strikes more terror than the word 'CANCER', and with considerable justification. Deaths due to cancer stand second place after heart disease in developed and developing countries. In the discussion that follows, some of the causes of this fear will be explored as well as sources of the reasons why graduated optimism is now justified for future.

Neoplasia literally means "new growth", and the mass of cells composing the new growth is a neoplasm. The term new growth does not adequately define a neoplasm. A much more meaningful definition is "A neoplasm is an abnormal mass of tissue, the growth of which exceeds, and is un-cordinated with that of normal tissues and persists in the same excessive manner after cessation of the stimuli which evokes the change" (Willis, R.A. 1952). To this characterisastion we might add that the abonormal mass is purposeless, preys on the host, and is virutally autonomous. It preys on host in so far as the growth of the neoplastic tissues competes with normal cells and tissues for energy supplies and nutritional substrate and thus neoplastic tissues render the host emaciated

and have the ugly potentials of rapid growth, invasion and destruction of contiguous structures, and dissemination through out the body, leading to death.

For centuries a bitter duel has been fought, as mankind has endeavoured by every available means to ward off most threatening enemy knwon to life: CANCER. Despite tremendous efforts, cancer has still not been truely checked, let alone conqoured. The basic question of the cause and course of the malignant disease is one on which it can be claimed, without exaggeration, that a great many advances have been made in recent decades. With these advances, the hope that cancer would ultimately prove to be amendable to various forms of therapeutic modilition i.e. surgery, radio therapy, chemotherapy and immunotherapy will turn to success in near future.

Recently, chemotherapy is playing increasingly important role in management of malignant diseases (cancer) particularly where surgery or radiotherapy can not give complete cure. Radiotherapy and surgery after ways of reducing the tumour mass in specific regions of the body make it amenable to surgical excision or high doses of radiotherapy. Neither is applicable to the destruction of widely disseminated or circulating tumour cells characteristically present in most patients with cancer. Chemotherapy can be tried in every form of malignant diseases either localised, disseminated or circulating tumour cells.

The chemotherapy of malignant disease refers to the use of cyto-toxic drugs. Cytotoxic drugs are general cellular poisons which have a deteriorating/deleterious effect, to a greater or lesser degree on normal cells and a variety of tumours. Because these are potentially lethal, cancer chemotherapy is largely a compromise between toxic and therapeutic effects. While instituting chemotherapy we need to consider seriously the relative differential sensitivity of normal versus cancerous tissue. So a basic goal of cancer chemotherapy is the development of agent which have "selective toxicity" against replicating tumour cells but which at the same time spare replicating host tissues. Such as ideal drug has not yet been found, and only the hormones and asparaginase and, to a lesser extent, mitotane (O, P, DDD: lysodern and streptozocin) approach this goal. Although these drugs have important side effects, their toxicity is not primarily directed against normal replicating cells.

The histologic diagnosis and extent of the disease frequently define the goal of therapy as either curative or palliative with or without likelihood for prolongation of survival and frequently determine the most appropriate treatment, surgery, radiotherapy, chemotherapy or combination of these.

Thus the therapeutic objective should be based upon

what can be accomplished by each mode of therapy. For example, the following disseminated cancers are curable by chemotherapy: most post-gestional chorio-carcinomas, many wilms, tumours and seminomas, some child-hood acute lymphoblastic leukaemias, adult and childhood lymphomas and some, testicular carcinomas in young men. For other neoplasms, chemotherapy may effort significant palliation and prolongation of life, even in advanced stages of breast, ovarian, endometrial, prostate, thyroid and cat cell cancers and for acute leukaemia, lymphomas, myeloma and macroglobilinemia. Some patients with colon or gastric carcinomas, sarcomas, and head and neck tumours may be relieved of symptoms by chemotherapy, but survival cannot yet be prolonged. Most patients with disseminated melanomas and lung, renal and pancreatic carcinoma are not objectively benefitted by systemic chemotherapy.

The choice of drugs in a particular combination rests primarily on clinical effectiveness and is essentially empirical. Choice of drug may be determined by the dose or dose schedule required. Single drug is used alone when a disease is sensitive to only one agent or its derivatives. Combination of drugs that block multiple biosynthetic pathways are given in an attempt to obtain a synergestic effect on the tumour. Thus, combination chemotherapy refers to the concurrent, to some extent sequential, use of several

drugs in an attempt to achieve maximum therapeutic effect without increasing unduely the undesirable side effects of the over-lapping toxicities. Formerly single drug regimen was followed where results were not good, but with combination chemotherapy results are increasingly encouraging (De Vita VT Jr. et al 1975).

The cyclic administration of mechlorethamine, vincristine, predinisone, and procarbazine ("MOPP") produce 81% complete remession of Hodgkin's disease in untreated stage 3 and stage 4; 76% complete remission after radiotherapy alone; 50% complete remission after prior radiotherapy and chemotherapy. 70% of complete responders were alive after 5 years, 50% were continuously free of disease during that period. Single agent therapy with these drugs is much less successful. (De Vita VT Jr. et al.; 1970).

In case of disseminated testicular cancer combination of bleomycin, vinblastine, and cis-platin accounted for 75% complete and 26% partial remissions (Einhorn LH et al; 1977).

Bone is a common site of metastatic disease of breast, prostate cancer & Hypernephroma. While frequency of bone metastasis is 1% to 2% at the time of diagnosis (Perez DJ et al; 1983, Rosing N et al; 1982).

Radiologic examination of the bones has been the standard method of investigation for years (Edelstyn GA et al; 1967; Bachman AL et al; 1954). Only few studies have elucidated the role that clinical examination and biochemical tests may play in the diagnosis of bone metastasis (Co Wan JD et al; 1981; Krishnamurthy GT et al; 1977, Coombes RC et al; 1983; Hortobagyi GN et al, 1984).

Bone marrow, too, is one of the most common location for prostate, breast, kidney, bronchial tree, thyroid cancers metastasis. According to some authors, skeletal metastasis are always preceded by bone marrow invasion (Willes R.A.; 1952). Consequently bone marrow biopsy, is a simple & relatively non invassive procedure, might prove useful for detection of micrometasis. So we can have adequate staging technique able to identify patients with micrometastasis, which would allow us to specifically select candidates for adjuvent chemotherapy.

Better results in recent years have been due to improved methods of applying cyto-toxic drugs as well as to introduction of new drugs and combination chemotherapy. New approaches are clearly needed to overcome the cancer problems with chemotherapy. As cancer is becoming increasingly common in Bundelkhand area and we are getting lots

of cases of malignancies in various stages, where surgery & radiotherapy have their role in combination with chemotherapy or alone and in late stages where previous two modalities have limited role (palliative). It was decided to try chemotherapy in all these groups to assess its role as curative or for palliation use.

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REVIEW OF LITERATURE

REVIEW OF LITERATURE

Cancer chemotherapy has its roots in World War I, when toxic effects of Mustard war gases over various systems especially over haematopoetic system (Spitz, 1948) were noticed when these gases were used as chemical weapons because of their varicant action on skin and mucous membrances. In 1918 at a base hospital in France, severe leukopenia was observed in patients nine days after they had been exposed to mustard gas (Krumbhaar, 1919). Eventually investigators recognised that these systemic effects might also reduce the number of malignant cells in certain cancers in particular, the leukaemia and lymphomas (Carter and Dershner, 1976).

In 1931 Adair and Bagg published the results of treatment with alcoholic solution of mustard gas (Di-chloro Di-ethyl sulphide). They referred to the observation of James Ewing and others on the destructive nature of burns caused by the gas and used it on tumours involving skin, it was applied topically in twelve cases and injected into the tumour in one, a recurrent neurogenic sarcoma. The tumours regressed and remission of a few months were obtained in other patients. Hopes were

expressed for the future use of mustard gas in cases of localised malignancies.

Chemically the nitrogen mustards differ from mustard war gases only in that a nitrogen replaces sulphur (Wintrove, et al; 1947). In the early 1940's under the office of Scientific research and development with chemical warfare service of the United States Army, extensive investigation of the toxicology of nitrogen mustard were made (Burchenal, J.H. et al; 1948). In 1942 Goodmann and Gillman had studied the pharmacology of nitrogen mustard derivatives (Methyl chloro ethyl amine) and noted their effects on lymphoid tissues and dividing cells. The two compounds which received attention were known by the code name HN_2 and HN_3, the later trichlorotriethylene being the first to be used clinically (Goodmann et al; 1946). Clinical trials with HN_2, mustine Hydrochloride (Nitrogen mustard, Mechlorethamine hydrochloride), were initiated in 1943 in the united states and results were reported by RHOADS, 1946. finally in 1945-46 during early clinical trials at an Army Hospital, Nitrogen mustard was demonstrated to be the first chemotherapeutic agent used, to successfully treat Hodgkin's disease (Cook, W.L., et al 1950). During the same time period, the antimetabolites were developed when the researchers

discovered that slight modification of the structure of Folic acid made it a growth arresting metabolic antagonist. Farber et al begain clinical trials with Folic acid antagonist in 1940's and studied the effect of Folic acid metabolism on leukaemic cells resulted in the second cytotoxic drug of therapeutic value the antifolate (antimetabolite) Methotrexate.

Thereafter many naturally occuring substances were listed for anti tumour activity in experimental models, many of them are in clinical use now.

SCIENTIFIC BASIS OF CHEMOTHERAPY

QUANTITATIVE KINETIC APPROACH :

Since in most instances qualitative metabolic differences between normal and neoplastic cells have not been discovered, the chemotherapist must plan according to quantitative differences in the proliferative kinetics of normal and Neoplastic cells growth of tumour regression without major host toxicity is to be achieved.

THE CELL CYCLE :

Through the use of radioactive labelling of the nitrogenous base, thymidine, in the early 1950's, it become apparent that DNA synthesis is not constant between periods of Mitosis, had been thought, but there

is a distinct gap in interphase both before and after the period of DNA formation. This information led to the development of the cell cycle model which comparises of the following stages:

M - Period of cell division.

G_1 - Postmitotic period, in proliferative cycle (RNA, and protein synthesis).

G_o - Post mitotic period, temporarily out of proliferative cycle, "resting cells" - when stimulated, cells move into G_1 and begin to multiply again.

S - Period of DNA synthesis.

G_2 - Premitotic period (RNA and protein synthesis). For a given cell line 'S' (Synthetic phase), 'G_2' (Premitotic phase) and 'M' (Mitotic phase) are nearly constant, when 'G_2' phase is very long the cells can be considered to be in 'G' resting phase.

CELL SPECIFICITY OF ANTINEOPLASTIC AGENTS :

Chemotherapeutic agents may be classified into the three general types based on the stage of the cell cycle at which they exert their major effects.

CELL CYCLE SPECIFIC AGENT :

These agents exert their effects as long as the cells are dividing they are not cytotoxic to the cells

in the resting 'G_o', stage but are toxic to cells in any other cell cycle stage.

PHASE SPECIFIC AGENTS :

These agents exert their effects only when the cells are in a specific phase (or stage) of the cell cycle. Some agents, such as the vinca alkaloids, are cytotoxic only when the cells are in the M-phase, while others whose principal action is inhibition of DNA synthesis, are toxic to cells only when they are in the S-phase. Hydroxy urea and cytosine arabinoside are in this category. Some agents are only relatively S-phase specific; this means that besides being able to inhibit DNA synthesis, they also can inhibit RNA and protein synthesis. The result is a slowing of the cell cycle with prevention of cells from entering the more sensitive S-phase. Methotrexate, 5FU, -6TG, and 6-MP appear to exert their effects in this manner.

CELL CYCLE NONSPECIFIC AGENTS :

Cell cycle nonspecific agents are effective when cells are dividing as well as when they are in the resting (G_o) stage these agents exert their effects directly on DNA, and therefore their activity is not enhanced by administering these drugs in the S-phase (Horton and Hill, 1977). Nitrogen mustard, dacarbazine, and mitomycin appear to be in this category (Baserga, 1965).

RATIONALE FOR CHEMOTHERAPY :

Regardless of whether the intent of chemotherapy is partial response and short term palliation, complete remission with prolonged survival, or cure, there are many principles that govern the use of cancer chemotherapeutic agents :-

1. A single cancer cell is capable of proliferating exponentialy to form a tumour mass, breaking away from the mass and travelling via the lymphatics and blood stream to other body sites where it can proliferate to form another tumour mass (metastatic disease). By this method it eventually can kill the host.
2. As a tumour mass increases, the time it takes the tumour to double in size, the "Doubling time" depends on three factors (March and Mitchell, 1974).
   (a) The time it takes a cell to complete one cycle of growth and division (its "generation time").
   (b) The fraction of cells undergoing division.
   (c) The tumour's "cell death" rate.

   Because of the inter play of these factors it can not always be assumed that a small tumour is an early tumour (Silver et al, 1977).

3. Cure is accomplished only when the last cancer cell has been eradicated by surgery, by radiation therapy, or by chemotherapy - either alone or a combination of these - with or without the benefit of the host's own defense mechanisms.

4. Assuming that all kinetics, biochemical, and Pharmacological factors are constant, most cancer chemotherapeutic agents in any given dose kill the same percentage, not the same number of cells. For example, if a chemotherapeutic agent with an 80% kill rate is administered into someone with a tumour consisting of one million cells, then after the first dose 800,000 cells are killed and 200,000 remain alive. Assuming there is no regrowth, after a second dose 160,000 are killed and 40,000 remain alive, and after a third dose 32,000 cells are killed and 8,000 remain, and so on. Thus, the same dose generally will kill the same percentage of cells regardless of whether the tumour is large or small. However, this is not strictly true, because of the variable number of cells in cycle as tumours size changes and because of poorly understood chemical changes and resistant subpopulations that emerge

during the course of chemotherapy.

5. Although chemotherapeutic agents are more toxic to malignant cells than to normal cells (called selective toxicity), the hosts normal cells will experience some degree of injury. the rapdily renewing cell populations, such as those of the gastrointestinal (GI) tract, Bone marrow, and hair follicles are those that are most likely to be affected.

6. Benefits of treatment with chemotherapeutic agents must outweigh the side effects.

7. Antineoplastic agents are frequently given in intermittent course of therapy(every 1 to 8 weeks) to allow restoration of the number of normal cells that were affected by chemotherapy. During this waiting time between treatments, the cancer cell population also increases but, with successful chemotherapy, remains smaller than what the population was prior to the initiation of chemotherapy. Successful chemotherapy (cure) implies reduction of the cancer cell population with each successive treatment. Chemotherapy is considered to be unsuccessful if, during this period of waiting for the patient's normal cells to recover from the

cytotoxic effects of the drugs, the tumour cell population recovers and grows to a number that is more than the starting number of cells. Survival time may be prolonged even though this occurs, but if there is a successive increase in cancer cell population with successive course of treatments, eventually a fatal number of cancer cells is reached and death occurs (Silver et al; 1977).

8. Cancer chemotherapy is most effective when the tumour burden is small (less than 10^9 tumour cells) and there is no clinical evidence of disease.

9. some tumours produce biochemical markers that indicate the presence of disease when there is no clinical evidence of disease present. Examples are the production of abnormally high levels of human chorionic gonadotropin (HCG) in patients with choriocarcinoma and 5-hydroxyindoleacetic acid (5-HIAA) in patients with carcinoid tumours classification of chemotherapeutic agents.

IN ANTI METABOLITE GROUP :

Purine analogues as an anti metabolite was developed and the role of mercaptopurine as an antimetabolite was

shown by Burchenal and others in 1953. The Pyrimidine analogue fluoro-uracil (5-Fluoro-uracil) was used clinically in 1958 (Heidel berger et al; 1963) and later thioguanine and others were tried and introduced into clinical use. Cytosine arabinoside was also shown to possess antitumour activity by Evans et al, 1961. A new flourinated pyrimidine (Ftorafur) has been developed in the U.S.S.R. which has been extensively listed in Japan, and is now under evaluation in the U.S.A. (Blokhina et al; 1972).

ALKYLATING AGENTS :

In this group Mustine and trichlorotriethylamine were used parenterally (Goodmann et al, 1946, Rhoach, 1946). The first oral alkylating agent used clinically was tretamine (tri-ethylene - melamine, TEM) and a series of oral nitrogen mustard derivatives were synthesized at the Chester Beatty Research Institute London. Chlorambucil, Melphalan (Haddow and timmis, 1953) are still widely used. Thiotepa (triethylene thio-phosphoramide) was used as an adjuvant to mastectomy in a rational co-operative study under the direction of the National Institute of Health, with doctor Rudoflf Noer as Chairman 1964.

ANTIBIOTICS :

Antibiotics were also being investigated for antitumour activity. Actinomycin D from a strain of Streptomyces was shown to have antitumour activity in animals

(Schulte 1952; Waksman, 1960, Faber et al, 1960; Faber, 1966). Almost at the same time Mitomycin C was developed in Japan (Frank et al, 1960). Daunomycin (Daunorubicin) was studied by Di Marco et al, 1963. While Adriamycin was reported to have antitumour activity in Sarcoma by Bonnadonna et al; 1969. Later, Adriamycin was utilized for thyroid cancer (Gottliep, 1972). Bleomycin has been used to successfully cure testicular tumours (Blum et al, 1973).

ALKALOIDS AND NITROSOUREAS :

These agents were of special interest to the scientists. Vincristine and Vinblastine were shown to be successful in treatment of Hodgkin's disease and other tumours by a number of workers (Holes at al, 1960; Johnson et al, 1960; Warwick et al, 1960). In 1972 a new plant alkaloid VM 26 (Citrovorum) was reported to be effective in lymphoma, glioblastoma (Sklansky et al, 1973) and intracerebral L1210 leukaemia (Muggia, et al, 1971). Among Nitrosoureas, carmustine (BCNU), Lomustine (CCNU) and Semustine (Methyl CCNU) have been shown to have variable response rate in advanced gastro intestinal cancer (Moertel, 1973), while streptozoticin is the only drug which has been meaningfully evaluated in carcinoma of Pancreas (Broder and Caster, 1973).

MISCELLANEOUS AGENTS :

Many miscellaneous agents have been shown to possess antitumour activity. OP'DD (Mitotane) is an established agent for adreno-cortical carcinoma (Bergenstal, et al, 1960). Hydroxy urea has a place in the treatment of chronio myelocytic leukaemia (Kennedy and Yarbro, 1966). Unique among Chemotherapeutic drugs is an enzyme L-asparaginase (Broome, 1968) useful in the treatment of acute lympho-cytic leukaemia (Burchenal and karnofsky 1970; Cohen et al, 1976; Editorial, 1971). Hexamethylmelamine and Dacarba-zine (DTIC) are of importance in having anti-tumour acti-vity against ovarian carcinoma and malignant melanoma (Wilson, 1970; Luce et al 1970). Procarbazine, a methyl-hydrazine derivative, act like an alkylating agent and is used in leukaemia, Hodgkin's disease and brain tumours (Spiers, 1967; Vasantha et al, 1974): the ability of some platinum complexes to inhibit cell division led to their investigation as anticancer drugs by Rosenberg and others in 1985. Cis-platinum (Platinum diamminodichloride, cis-diammine platinum II) has been most extensively used, & is highly effective in testicular tumours and ovarian carcinoma (Gottlieb and Drewinko 1975; Hill and Baserga, 1975).

NEW DRUGS :

Dibromo mannitol and 5- azacytidine have been demonstrated useful in leukaemia (Cancellos, et al, 1975; Vogle 1975). The drugs in study for phase I and II would be the new active drugs of tomorrow.

In alkylating agents, Iphosphamide is a cyclophosphamide analogue under trial for ovarian cancer, breast cancer and lymphomas (Cohen, et al, 1973; Ahmann et al, 1974). Asaley, a derivative of Melphan (Phenylalamine mustard) and calactitol, a derivative of dihalohexitol have shown response in lymphoma and breast carcinoma (Elson et al, 1968). Anti metabolites Baker's antifol, a triazine antifolate (Skeel et al 1974; Rodrigaez et al 1975), Cyclocytidine (NSCI 45668) a synthetic analogue of cytosine arabinoride (HO et al, 1974, Chawla et al 1974) and Diglycoaldehyd, a product of purine nucleoside, inosine (Kaufman and Mittielman 1975) are under clinical trial for different malignancies. Antitumour antibiotics chromomycin and piperazinedione isolated from a culture of streptomyces are being clinically tested in Japan, South Africa and United States (Slavick and carter 1973; Kovach and Moertel 1973; Gottlieb et al 1975; Pratt et al 1975) Random synthetics cytembena (NSC 104801) and Laetrite (Amygdalin) are under observation (Carter, 1976; Frytak et al 1975; Moertel et al 1982).

At present, there are around 40 effective anti-neoplastic drugs available. The quest for new cytotoxic drug continues with optimism and there is still greater potential for the better application of available agents.

COMBINATION CHEMOTHERAPY :

In 1964 the simultaneous use of vincristine methotrexate, murcaptopurine and Prednisone, the so called VAMP regimn in acute lymphoblastic leukaemia of childhood led the way to combined chemotherapy in other forms of malignant disease (Freidreich et al, 1964; Henderson, 1967; Henderson 1969). By combination chemotherapy maximum therapeutic effects can'be achieved without increasing unduly, undesirable side effects (Carter & Sober, 1974; De vita and Scheir, 1973; De Vita et al, 1975).

THE FIVE GENERAL PRINCIPLES GOVERNING THE USE OF COMBINATION CHEMOTHERAPY ;

1. Each drug in the combination should have been demonstrated to have some activity on its own against the tumour type for which the combination is being used.
2. Drugs with a similar mechanism of action should not be combined.
3. As far as possible the major dose-limiting toxicity

of each drug should differ from that of the other component of the combination.

4. since it is rarely possible to avoid some overlap in toxicity to host tissues, it is usually necessary to reduce the dose of each of the component drugs compared with the optimal dose which would be used if the drugs were prescribed individually.

5. There should be no known adverse interaction between the drugs (J.F. Smyth, 1984).

RATIONALE OF USING INTERMITTENT COMBINATION CHEMOTHERAPY :

This is based on the two groups of facts :-

(i) Different constituants of combination chemotherapeutic agents.

- Have different biochemical sites for action in the cell.
- Attacking cells at different phase of growth cycle.
- Synchronize the active cell cycle.
- Emperically.

(Lawrance DR: and Bennett, PN : 1980).

(ii) When drugs are used together in full doses, intermittent treatment at intervals of 2-4 weeks rather than continuous daily administration has been employed. Such an approach has two theoretical advantages.

- First is that if a treatment programme exert to selective killing effect on tumour tissues over normal bone marrow, an interval of about two weeks is usually sufficient to allow the recovery of bone marrow to pretreatment levels without allowing regrowth of tumours population to tumours population to base line levels.
- The second advantage is that interval scheduling may permit the recovery of the host's immunological mechanisms -between cycles of chemotherapy. (De Vita, VT Jr, 1983).

In many situations, cytotoxic drugs are capable of reducing only a fraction of tumour mass, that is why chemotherapy is adjuvant to surgery and or radiation therapy to lessen the total tumour load. Amongst the first reports Mrazek et al (1959) showed the use of nitrogen mustard post operatively in colo-rectal carcinoma. Since then many institutes/workers have been continuously reporting successful use of adjuvant chemotherapy e.g. Noer (1961) for breast cancer; Longmira et al (1968) for gastric carcinoma, Holden et al (1970) for colorectal cancer.

Since 1971 multi modality treatment has advanced as much that even 100% cure has been achieved in some cases

like in GIT cancers, sarcoma, of paediatric age group, wilms tumour, Ovarian Carcinoma, Bronchogenic and Breast carcinoma.

Clinical trials have demonstrated that cancers can generally be grouped into categories according to the effectiveness of systemic treatment (Vincent, T.,De Vita, 1984). Malignant diseases can be ranked into group comprising those for which chemotherapy contributes to cure, those for which effective control prolongs useful life and those for which benefit is less certain or unproven.

I. TUMOURS FOR WHICH CHEMOTHERAPY CAN BE CURATIVE ;

- Acute lymphoblastic leukaemia (childhood)
- African Burkitt's lymphoma.
- Hodgkin's disease.
- Wilm's tumour.
- Non-Hodgkin's lymphoma (Diffuse histiocytic and nodular mixed type).
- Testicular carcinomas (Teratomas)
- Ewing's sarcoma
- Rhabdo myosarcoma
- Chorio carcinoma

II. TUMOURS IN WHICH CHEMOTHERAPY PROLONGS LIFE. (RESPONSE RATE 50%)

- Acute Leukaemia (adult)

- Breast carcinoma
- Chronic leukaemia
- Myeloma
- Ovarian carcinoma
- Small cell lung cancer
- Osteoganic sarcoma
- Non Hodgkin's lymphoma (lymphocytic type).

III TUMOURS IN WHICH CHEMOTHERAPY SOMETIMES PROLONGS LIFE (RESPONSE RATE 50%)

- Head and Neck tumours
- Gastro intestinal carcinomas
- Bladder carcinoma
- Hypernephroma
- Endometrial carcinoma
- Malignant Melanoma.

IV. TUMOURS WHICH ARE USUALLY REFRACTORY TO CURRENTLY AVAILABLE CHEMOTHERAPY.

- Carcinoma oesophagus
- Colo-rectal carcinoma
- Squamous cell lung carcinoma

Clinical experience with alpha interferon-26 has shown marked therapeutic activity in hairy cell leukaemia. Interferons also have potential role in combination with cytotoxic drugs for treatment of multiple myeloma, cutaneous

T cell lymphoma, chronic lymphocytic leukaemia and among solid tumours, viz, melanoma, renal carcinoma and ovarian carcinoma (Spiegel, 1986).

RECENT ADVANCES IN CANCER CHEMOTHERAPY :

The ability to induce complete remession in Adult Acute leukaemia has improved dramatically over the past two decades. In this reference high dose continous infusion of cyclophosphamide, cytrabine, vincristine and pridnisone demonstrate, promising efficacy with minimal toxicity in referactory Adult acute leukaemia (Guttrie, 1987).

In 1988 Lo Russo et al, showed in a trial study of ten year that a combination of 5 FU/cisplatin & Bleomycin is most effective in management of paranasal sinuse carcinoma.

The result of the study conducted by Koga et al, 1988 prophylactic therapy of peritoneal recurrence of gastric cancer by continuous hyperthemic peritoneal perfusion with Mitomycine 'C' is simple, safe & effective.

Use of combined peripheral and central chemoembolization of liver tumours improves the survival in patient with primary and secondry liver tumours (Shimamura et al, 1988).

Combination chemotherapy regimen consisting of

Adriamycin & Mitomycin 'C' is an effective regimen for treating patients of breast carcinoma, previously treated with CMF (Colozza et al, 1988).

combined modality of treatment with infusion of 5 FU, Mitomycin 'C' and Radiation is an effective & well tolerated treatment for adenocarcinoma of oesophagus and gastrooesophageal junction in advanced cases (Coia et al, 1988).

The combination of 5 FU, Adriamycin and cisplatin is an active combination for the treatment of metastatic adrenal cortical carcinoma (Schlumberger et al, 1988).

Combined treatment for advanced oral cavity cancer by combination of Neomycin, Vincristine, Mitalactol, Prednisone, and Methotrexate with leucovorin rescue followed by surgery appears both safe an promising treatment (Olasz et al, 1988).

Adjuvent chemotherapy for low stage non seminomatous germ cell tumour of the testis with vascular invasion offers good results (Sanderman & Yang 1988).

Combination chemotherapy with cyclophosphamide, Adriamycin and vincristine is active in malignant thymoma

and myasthenia gravis (Kosmidis et al, 1988).

Combination of ois platin & Mitoguazone for induction chemotherapy in advanced head and neck cancers, gives good results (Forastiere et al, 1988).

Platinum programme may provide useful palliation for selected patients suffering from neoplasms arising from salivary glands and contiguous structures in head and neck (Caregan et al, 1988).

Management of stage III primary breast cancer with primary chemotherapy, surgery & radiation therapy rendered most patients disease free & produced excellent local control rate (Hortobagyi et al, 1988).

High dose cyclophosphamide in treatment of refractory lymphomas and solid tumour malignancies may be given with acceptable toxicity in heavily pre treated patients (collins et al, 1989).

Low dose cytosine Arabinoside may be worthy of trial in patients with secondary acute non lymphoblastic leukaemia and myelodisplastic syndrome with resistant cases (Kumar et al, 1989).

High dose cisplatin may benefit selected patients

with inoperable advanced head and neck tumours (Havlin et al, 1989).

The present gains are sufficiently promising that for a few tumours it may be possible with present knowledge, by the rational combination of several drugs, or of drugs concurrently with surgery and X-radiation, to expect more complete control over cancer. Yet the cancer therapy has still a very vast arena to be explored by mankind, for mankind in times to come.

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MATERIAL AND METHOD

MATERIALS AND METHODS

In the present study, a concerted effort has been made to evaluate the role of chemotherapy in ninty patients, having various malignancies, who were thought to be candidates for chemotherapy and were admitted in M.L.B. Medical College Hospital, Jhansi.

SELECTION OF PATIENTS :

Criteria for selection of patients for inclusion in the study was objective. Patients suspected of having malignancy were admitted to hospital. They were subjected to thorough clinical examination including detailed history and physical examination. Relevant investigations were made to confirm the diagnosis, as well as for classification and staging of malignancy. In all cases diagnosis was confirmed by histopathological examination. Staging of the disease was done according to INM CLASSIFICATION. After the diagnosis and staging, patient was assessed for chemotherapy according to type and stage of malignancy and then trial of chemotherapy was begun. Those cases were selected for chemotherapy, who

either were found unfit for radiotherapy or surgery, due to extensive spread of the disease or where disease had recurred after Radiotherapy or surgery.

CLINICAL CLASSIFICATION AND STAGING : was done to plan treatment strategy and to evaluate prognosis. Standardized nomenclature given by UICC, known as the TNM system was used to know anatomic extent of disease.

T - extent of primary tumour (T_o, T_{1-4}).

N - condition of regional lymph nodes (N_o, N_{1-4})

M - Absence or presence of distant metastasis (M_o, M_{1-4}).

After arranging T, N and M categories (with degrees of extent), these were then grouped into four clinical stages (e.g. I to IV). Alternatively typical clinical staging was done as follows :

Stage	Primary tumour (T)	Regional Lymph nodes (N)	Distant Metastasis (M)
I.	Mobile (Operable)	None	None
II.	Mobile (Operable)	Mobile (Operable)	None
III.	Fixed (unoperable)	Fixed (unoperable)	None
IV.	Any of above	Any of above	Present

Depending upon organ involved, type of malignancy and stage of malignancy, following groups of patients were made:

1. Lymphomas - A. Hodgkins
   B. Non-Hodgkins
2. Leukaemias - A. Acute - Lymphocytic ALL
   Myelocytic AML
   B. Chronic - Lymphocytic CLL
   Myelocytic CML
3. Carcinoma Breast
4. Gastro-intestinal carcinoma A. Gastric carcinoma
   B. Colorectal carcinoma
   C. Pancreatic carcinoma
   D. Gall bladder and liver carcinoma.
5. Urogenital Carcinoma
   A. Ovarian carcinoma
   B. Testicular carcinoma - Seminoma
   Teratoma
   C. Renal carcinoma
   D. Prostatic carcinoma
6. Miscellaneous
   A. Lung cancer
   B. Head & Neck cancer.

SELECTION OF DRUGS/REGIMEN - There are different drugs and regimens described for various groups of malignancies in this study, a regimen was chosen after following consideration.

1. simplicity - Regimen with minimum number of drugs involved was chosen.
2. Availability of drugs - Drugs easily available locally were chosen.
3. Cost consideration - As the patients usually had spent a lot of money already in the treatment, many patients could not afford costly drugs. Therefore, regimen was chosen to give maximum benefit with alternate cheap drugs.
4. Side effects/Toxicity of drugs - Serious undesirable side effects were determining factors in the choice of a drug. For example, neuropathy caused by Vincristine limited its use, especially in the older patients. Vinblastine was similar and could be used instead. Daunorubcin and Adriamycin were cardio toxic.
5. Route of Administration - The oral route was convenient but insuitable when high doses were required. High dosage usually had an emetic effect hence a parenteral preparation was prepared when high dose were indicated. An oral drug could not be given to a patient who was vomiting, unconsicous or dysphagic. When there was doubt about the patient's reliability in taking medication the intravenous route was better method of administration. Intravenous preparation could cause

a severe local inflammatory reaction if they leaked from the vein into the tissues. Pain and swelling could persist at the site for a couple of weeks and the vein itself became thrombosed.

6. Drug dosage and schedule - the treatment objective was to provide the patient with the maximum therapeutic benefit and the minimum amount of morbidity. the relationship between the desired and undesired effects of a drug was termed as its "therapeutic index". Drug dose was chosen within a narrow range because of the dose response relationship and the low therapeutic index for most anti-tumour drugs. Depending on tolerance, dose adjustment were made for subsequent course of chemotherapy.

7. Sensitivity and Resistance to Drugs - might be primary, (natural) acquired or developing during course of treatment. So history of previous drug treatment was taken to overcome sensitivity or resistance to drugs.

TREATMENT PROGRAMMES

1. SINGLE DRUG CHEMOTHERAPY -

Single drug was used alone when the disease was found sensitive to only one agent or its derivatives with little or no clinical sensitivity to other types of drugs. Single drug was also used alone when no extra

advantage with drug therapy was expected.

2. MULTIDRUG/COMBINATION CHEMOTHERAPY -

Concurrent or sequential use of multiple drugs was made to achieve maximum therapeutic effect without increasing side effects. Drug combination was made with following criteria.

- Each drug should be active when used alone.
- Each drug should have different mode of action.
- Toxic side effects of each drug should differ.

Various regimens used for different malignancies are described ahead.

3. MULTI MODALITY THERAPY (ADJUVENT CHEMOTHERAPY)

Chemotherapy was used after primary resection to prevent the growth of sub clinical micro-metastasis or prior to local therapy with surgery to reduce a tumour bulk. So multi modal therapy was given by combining surgical and/or radio therapeutic approaches with chemotherapy.

Various drugs/regimens used for different malignancie are as follows :-

1. CARCINOMA BREAST -

A. For early Breast cancer (Adjuvant chemotherapy)

CMF Regimens

Cyclophosphamide 100 mg/m^2 oral days 1 to 14

Methotrexate 40 mg/m^2 I.V. day 1 & 8

Flurouracil 600 mg/m^2 I.V. day 1 and 8

Repeated after 4 weeks.

Such six cycles were given .

B. For Advanced Breast cancer -

(I) CMF Regimen

Cyclophosphamide 900 mg/m^2 I.V. day 1

Methotrexate 50 mg/m^2 I.V. day 1

Flurouracil 600 mg/m^2 I.V. day 1

Repeated after 3 weeks.

Such six cycles were given.

(II) Cooper's Regimen (CMFVP)

Cyclophosphamide 80 mg/m^2 oral daily

Methotrexate 20 mg/m^2 I.V. weekly

Flurouracil 500 mg/m^2 I.V. weekly

Vincristine 1.0 mg/m^2 I.V. weekly

Prednisone 30 mg/m^2 oral daily

(taken after 12 days)

Course was given for six weeks.

LYMPHOMAS -

A. Hodgkin's disease (Stage III and IV)

(i) MOPP regimen

Mustine HCl	6 mg/m^2 I.V. days 1 and 8
Oncovin (Vincristine)	1.4 mg/m^2 I.V. day 1 and 8
Procarbazine	100 mg/m^2 oral days 1 to 14
Prednisone	40 mg/m^2 oral days 1 to 14

Predinsone was given in Ist & 4th cycle only.

Treatment free interval 14 days(so one cycle was of 28 days).

Such six cycles were given.

(ii) COPP Regimen

Cyclophosphamide	600 mg/m^2 I.V. day 1 and 8
Oncovin (Vincristine)	1.4 mg/m^2 I.V. day 1 to 8
Procarbazine	100 mg/m^2 oral days 1 to 14
Prednisone	40 mg/m^2 oral days 1 to 14

Prednisone was given in Ist and 4th cycle only.

Treatment free interval 14 days (so one cycle was of 28 days).

B. Non Hodgkin's lymphoma

CVP Regimen

Cyclophosphamide	400 mg/m^2 oral days 1 to 5
Vincristine	1.4 mg/m^2 I.V. day 1 only
Prednisone	100 mg/m^2 oral days 1 to 5

One cycle consists of 21 days (so treatment free interval was of 16 days).

3. LEUKEMIA

A. Acute Myeloid leukemia (AML)

(I) For induction of remission

Cytosine arabinoside	100 mg/m^2 I.V. 24 hrs during days 1 to 3
Vincristine	1.4 mg/m^2 day 1
Daunorubicin	60 mg/m^2 I.V. days 1 to 3

Cycle repeated after 2 - 4 weeks.

(II) For consolidation and maintenance of Remission

Cytosine arabnoside	100 mg/m^2 I.V. 24 hrs. drip x 2 days.
Vincristine	1.4 mg/m^2 I.V x 2 days
Daunorubin	60 mg/m^2 I.V. x 2 days

Course was repeated every 8th week.

(III) For CNS involvement

Cytosine arabinoside	50 mg - Intrathecal twice a week
Methotrexate	0.15 - 0.25 mg/kg - Intrathecal twice a week (8 mg/m^2) max. dose 12.5 mg/m^2

B. Acute Lymphocytic leukemia (ALL)

(i) For induction of remission

Vincristine 1.4 mg/m^2 I.V. weekly

Prednisone 40 mg/m^2 oral daily

Given for 4 - 6 weeks.

For patients not responding to above treatment, added also Daunorubicin 25 mg/m^2 I.V. weekly x 3 weeks.

(ii) For Maintenance of remission

Methotrexate 25 mg/m^2 oral twice weekly

Mercaptopurine 50 mg/m^2 oral daily

Both are given for 3 months.

After every 3 months, vincristine and prednisone are given for two weeks in same dose and schedule as in Induction therapy.

Such cycles were given for atleast 2 years.

(iii) For CNS involvement

Prophylaxis methotrexate 12 mg/m^2 (Max. 15 mg) intrathecal

Preventive Methotrexate 12 mg/m^2 (Max. 15 mg) intrathecal twice weekly for 3 - 5 does.

C. Chronic Myeloid leukemia (CML)

(i) For indutction of Remission

Busulphan (Myleran) 4- 8 mg oral daily:

Given usually for 3 - 6 weeks (Max. 12 weeks)

Till TLC is 20,000/cmm.

For refractory cases - add

Mercaptopurine 50 mg/day for 5 days every week.

Given for 4 - 6 weeks.

(ii) For Maintenance -

Busulphan 2-4 mg oral daily.

Till TLC comes to 10,000-12,000/cmm.

Treatment was stopped when TLC was below 10,000/cmm.

Therapy was resumed when TLC INCREASED ABOVE 15,000/cmm.

D. Chronic Lymphocytic Leukemia (CLL)

(i) For induction of remission

Chloramucil 4-8 mg/day oral

Prednisolone 30-40 mg/day oral

Given for 6 weeks with adjustment of doses according to TLC report.

(ii) For Maintenance

Chlorambucil 2-4 mg/day oral

Predinsolone 15-20 mg/day oral

Given for 3-6 months (Prednisone was stopped after total 12 weeks).

4. GASTRO-INTESTINAL CARCINOMA

A. Gastric Carcinoma

(i) FAM Regimen

Flurouracil 500 mg/m^2 I.V day, 1,8, 21 and 28

Adriamycin 30 mg/m^2 I.V. day, 1 and 21.

Mitomycin C 10 mg/m^2 I.V. day, 1

Treatment free interval 4 weeks.

Such 6 cycles were given.

(ii) FM Regimen

Fluorouracil 325 mg/m^2 I.V. days, 1 to 5

Mitomycin C 1.5 mg/m^2 I.V. day 1

Treatment free interval 2 - 4 weeks

Course of six cycles

B. Colo-rectal carcinoma

Parenteral 5 FU 15-20 mg/kg I.V. once weekly

Oral - 5 FU 15 mg/kg daily for 6 days

Then 15 mg/kg once weekly.

C. Pacreatic carcinoma

(i) SMF Regimen

Streptozotacin 1 mg/m^2 I.V. day 1, 8, 29, 36

Mitomycin C 10 mg/m^2 I.V. day 1

Fluorouracil 500 mg/m^2 I.V. day 1, 8, 29, 36

Treatment free period 3 weeks (Duration of cycle 8 weeks).

(ii) FAM Regimen

Fluorouracil 600 mg/m^2 I.V. day 1, 8, 29, 36

Adriamycin 30 mg/m^2 I.V. day 1

Mitomycin C 10 mg/m^2 I.V. day 1, 8, 29, 36

Treatment free period 3 weeks (duration of cycle 8 weeks).

D. Gall Bladder and Liver

flourouracil 600 mg/m^2 I.V. or oral for 5 days

5. URO-GENITAL CARCINOMA

A. Ovarian Carcinoma (Stage III & IV)

CMF Regimen

Cyclophosphamide 150 mg/m^2 oral day 1 to 14

Methotrexate 40 mg/m^2 I.V. day 1 & 8

fluorouracil 600 mg/m^2 I.V. day 1 & 8

Rpeated every 4th week.

B. Testicular carcinoma

PVB Regimen

Cis platin 20 mg/m^2 I.V. day 1 to 5

Vinblastine 6 mg/m^2 I.V. day 1 & 2

Bleomycin 15 mg/m^2 I.V. weekly

Repeated after 3 weeks.

C. Renal Carcinoma

Renal cell carcinoma (Hypernephoroma)

(i) PROVERA (Medroxyprogesterone)

200 - 800 mg oral daily

400 - 800 mg I.M. monthly

(ii) Vinblastine 6 mg/m^2 I.V. once every two weeks

Wilms tumour (Nephroblastoma)

Actinomycin D 15 M gm/kg for 3-5 days

Repeated after 2 weeks.

Vincristine 1.5 mg/m^2 I.V. weekly

6 week course.

D. Prostatic carcinoma

(i) Diethyestilbestrol 5 mg/day 1-3 mg oral daily.

(ii) Honvan (Fosfestrol) 0.5-1, 0 gm I.V. daily x5 days

(iii) In hormonal refracting cases

Adriamycin 30 mg/m^2 I.V. day 1

Cyclophosphamide 100 mg/m^2 oral day 1 to 14

6. MISCELLANEOUS

A. Lung carcinoma

Small cell carcinoma

VAC Regimen

Vincristine 1.4 mg/m^2 I.V. day 1

Adriamycin 50 mg/m^2 I.V. day 1

Cyclophosphamide 750 mg/m^2 I.V. day 1

Repeated every 3 weeks.

B. Non smallcarcinoma

FAN Regimen

Fluorouracil 600 mg/m^2 I.V. day 1, 8, 29, 36

Adriamycin 30 mg/m^2 I.V. day 1

Mitomycin C 10 mg/m^2 I.V. day 1, 8, 29, 36

Treatment free period 3 weeks (Duration of cycle 8 weeks).

C. Head and Neck

(i) Methotrexate 50 mg/m^2 I.V. weekly

Bleomycin 15 mg/m^2 I.V. weekly

Course of 4-6 weeks.

(ii) Methotrexate 50 mg/m^2 I.V. weekly

Vincristine 1.4 mg/m^2 I.V. weekly

Course of 4-6 weeks.

FOLLOW UP AND SUPPORTIVE CARE

Patients coming for follow up of the therapy were subjected to following investigations specifically.

- Blood picture for pan-cytopaenia.

- TLC and DLC to exclude leucopaenia or Leucocytosis. Patients having TLC less than 3000/cmm were not given chemothe-rapy.

- Platlet count was done to see thrombocytopaenia. Chemotherapy was given while maintaining count above 1,00,000/cmm.

- Haemoglobin to exclude anaemia with strong therapy. Support to the patient was given on the following aspects.

- Treatment of fluid & electrolyte balance.
- Prevention and treatment of infection.
- Treatment of Haemorrhage and anaemia.
- Psychological supports

EVALUATION OF TREATMENT

In order to evaluate response to treatment following observations were made at each consultation and cycle of therapy.

- change in size of tumour.
- change in size of liver, spleen and lymphnodes etc
- change in weight and appetite.
- Change in symptoms like pain, pallor etc.
- Performance status of patient.
- Change in laboratory parameters.

CRITERIA FOR EVALUATION OF RESPONSE -

Three criterian of evaluation of response have been adopted.

1. Objective evaluation - was done in the following terms -

(i) Complete response (CR). Complete disappearance of the known disease, determined by two observations not less than four weeks apart.

(ii) Partial response (PR). 50% or more reduction in the sum of products of the longest perpendicular diameters of discrete measurable disease, with no new lesion appearing.

(iii) No responses (NR): Less than 50% reduction or no change in the size of lession or increase in the size of lesion or decrease in size of tumour less than 25%.

(iv) Progressive disease : Appearance of any new lesion, or 25% or more increase in size of previous lesion.

Duration of response is the period which lasts from the date when response was first recorded to the date there after on which subsequent response is noted.

2. Subjective evaluation was done on following parameters (Performance status scale, ECOG).

0 - Able to carry on normal activity.

1 - able to live at home with tolerable symptoms.

2 - Disabling symptoms but 50% of time in bed.

3 - Severely disabled 50% of time in bed, but able to stand.

4 - Very ill, confined to bed

5 - Dead.

3. Evaluation of toxicity - was done in three categories:

(i) Acute and sub-acute toxic effects-in which immediate (within seconds) and early (within hours) complications were observed.

(ii) Chronic and late toxic effects-to observe intermediate (within days) and late (within months) complications.

(iii) Death due to treatment.

PROCEDURES AFTER EVALUATION OF RESPONSE

On "Complete or partial response", the same chemotherapy, was continued.

On "No response" or "Progressive disease". the chemotherapy was altered in dose, schedule or components of regimen.

On toxicity, complications or side effects, the chemotherapy was either stopped or dosage were reduced or change in schedule or regimen was done with supportive care of patient.

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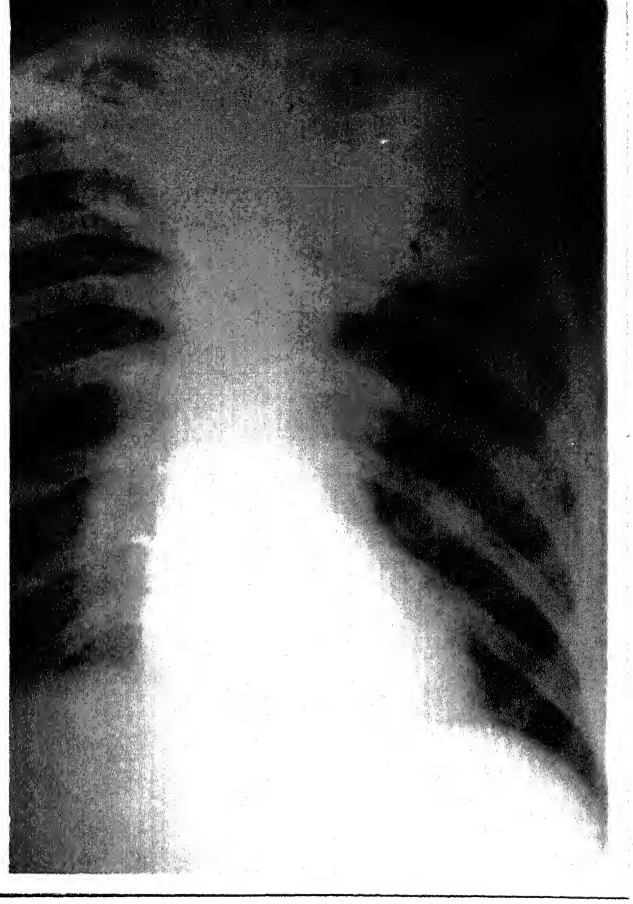
OBSERVATIONS

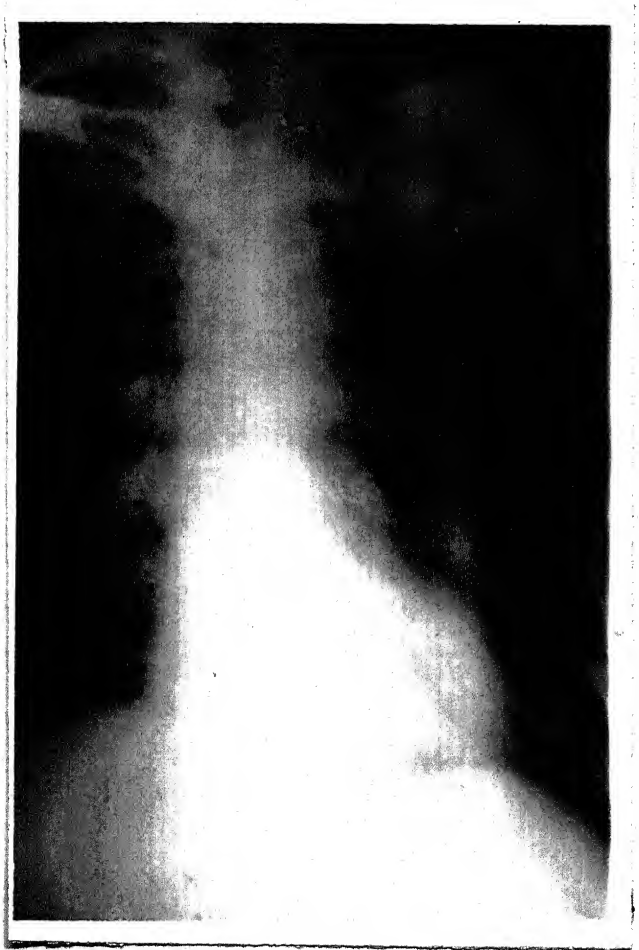
OBSERVATION

On the basis of preliminary diagnosis, patients suffering from malignant disease were admitted to the hospital wards of M.L.B. Medical College, Jhansi (U.P.). After thorough clinical examination, Lab. investigations, and other tests, ninety cases were selected as subjects for the present study. These patients were having malignances at different sites/organs and in varying stages and were treated by different chemotherapeutic regimens.



(a)

Carcinoma Lung b
(a) Before treatment
(b) After treatment



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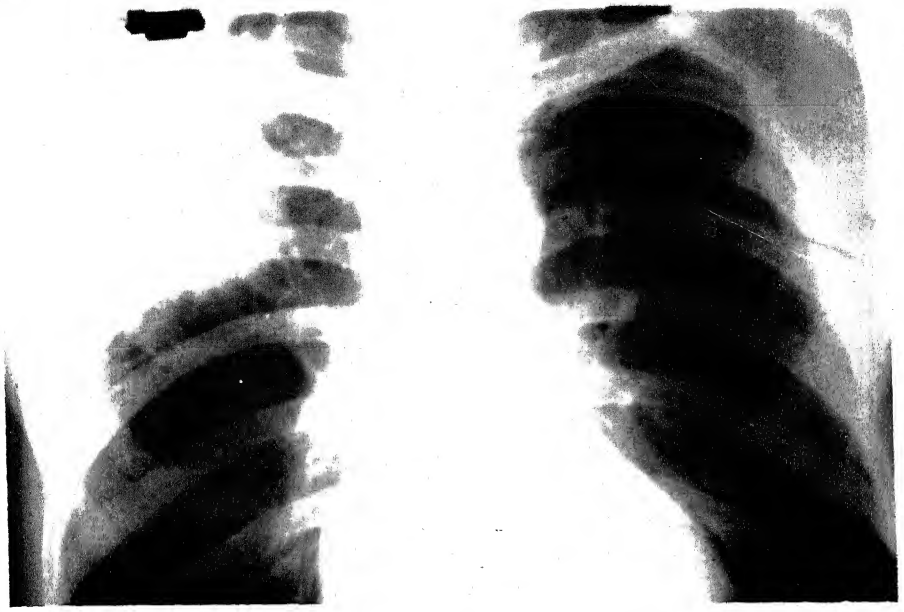
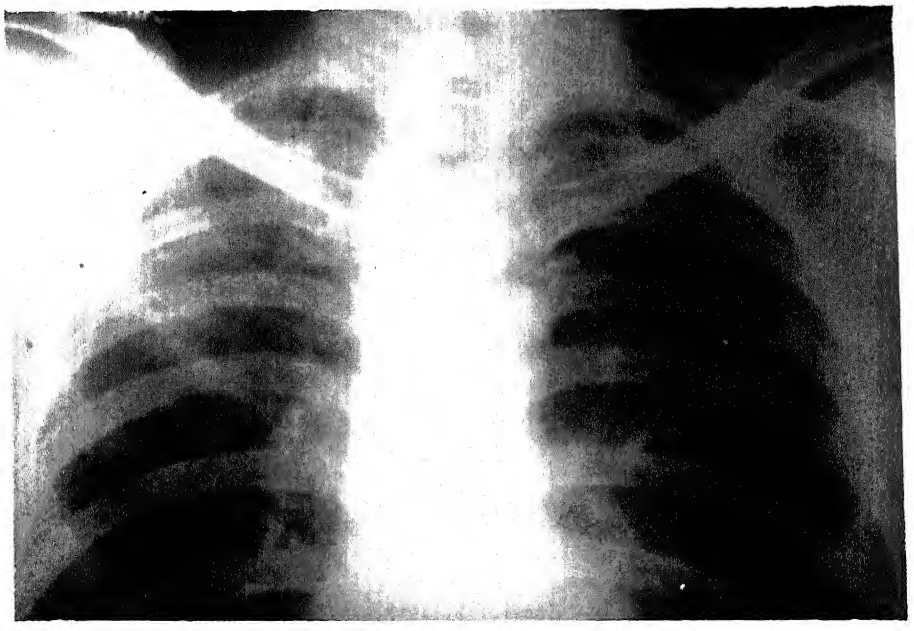


(a)

Carcinoma Lung Rt.
(a) Before treatment
(b) After treatment

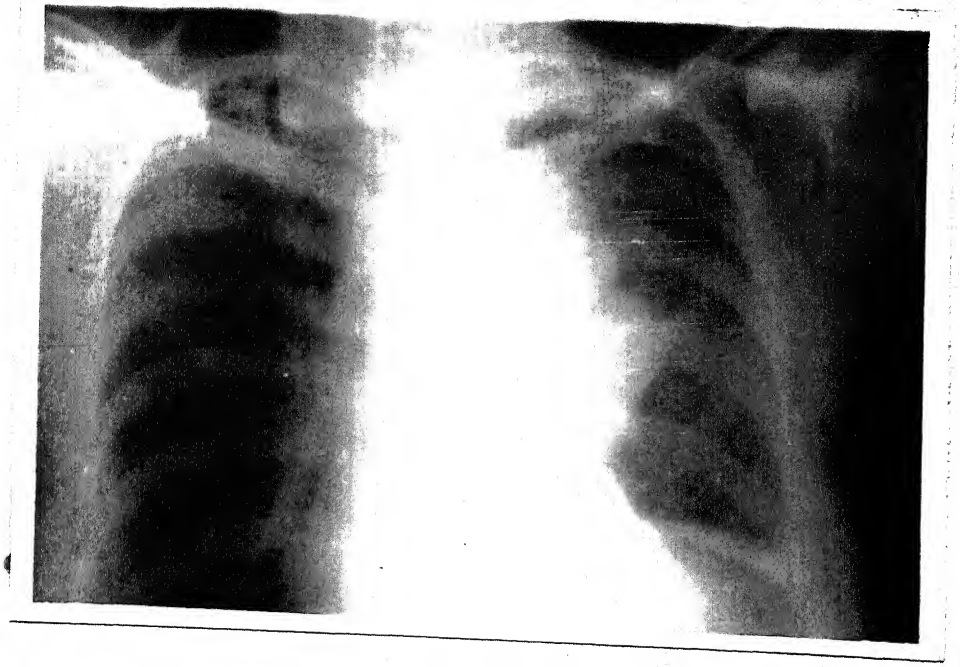


(b)

Table No II

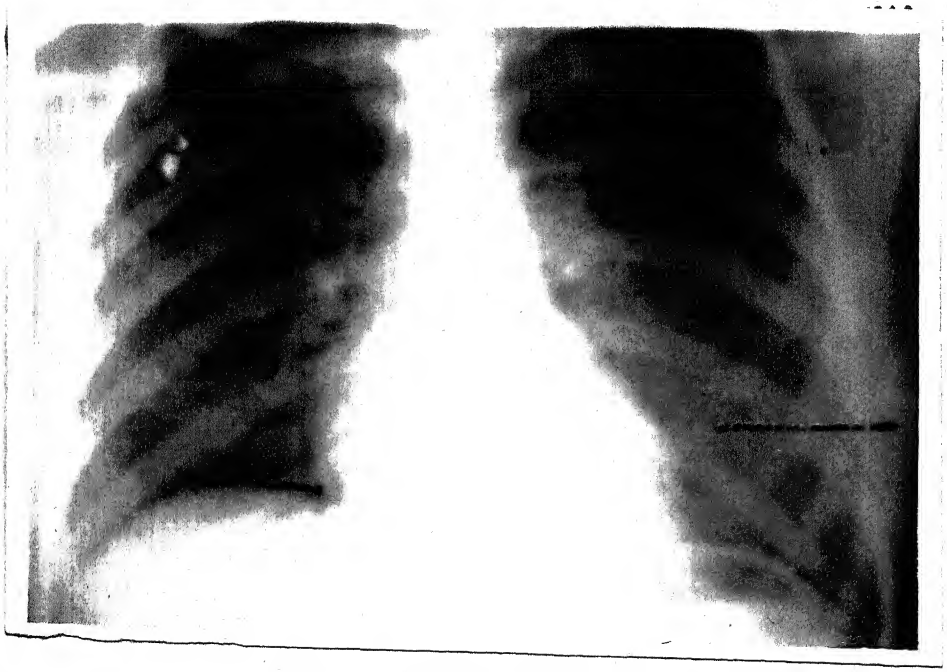
DISTRIBUTION OF CANCER IN VARIOUS AGE GROUPS :

MALIGNANCY	Type	NO. OF Pts.	AGE IN YEARS 0 - 10 No.	%	10 - 20 No.	%	20 - 30 No.	%	30 - 40 No.	%	40 - 50 No.	%	50 - 60 No.	%	60 - 70 No.	%
Ca. Breast	Early	11	-	-	-	-	1	9.09	4	36.3	1	9.09	3	27.27	2	18.18
	Late	5	-	-	-	-	-	-	1	20.00	1	20.00	2	40.00	1	20.00
Lymphoma	Hodgkin's	5	-	-	2	40.0	1	20.00	-	-	1	20.00	1	20.00	-	-
	Non-hodgkin's	4	-	-	-	-	1	25.00	-	-	1	25.00	-	-	2	50.00
	Burkitt's	1	-	-	1	100.00	-	-	-	-	-	-	-	-	-	-
Leukaemias	ALL	6	5	83.34	-	-	-	-	-	-	1	16.66	-	-	-	-
	AML	2	-	-	-	-	1	50.00	1	50.00	-	-	-	-	-	-
	CLL	-	-	-	-	-	-	-	-	-	-	--	-	-	-	-
	CML	7	-	-	-	-	4	57.16	1	14.28	-	-	1	14.28	1	14.2
G.I.T	Ca. Oesophagus	2	-	-	-	-	-	-	-	-	-	-	1	50.00	1	50.00
	Ca. Stomach	6	-	-	-	-	-	-	1	16.6	1	16.7	3	50.00	1	16.7
	colorectal Cancer	5	-	-	-	-	-	-	-	-	1	20.00	3	60.00	1	20.00
	Ca. Pancreas	2	-	-	-	-	-	-	-	-	-	-	2	100.00	-	-
	Ca. Gall Bladder & Lever	11	--	-	-	-	-	-	-	-	2	18.8	3	27.27	6	54.5
Uro-genital	ovarian Cancer	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Ca. Testis	2	-	-	-	-	1	50.00	-	-	-	-	-	-	1	50.00
	Ca. Kidney	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Ca. Prostate	43	-	-	-	-	-	-	-	-	-	-	1	33.3	2	66.7
	Ca. Bladder	4	-	-	-	-	-	-	-	-	-	-	2	50.0	2	50.0
Miscellaneous	Oral cancer	4	-	-	-	-	-	-	-	-	-	-	3	75.0	1	25.00
	Ca. Head & Neck	6	--	-	-	-	-	-	1	16.7	1	16.7	1	16.7	3	50.0
	Ca. Lungs	4	-	-	-	-	-	-	-	-	2	50.00	2	50.0	-	-
	TOTAL	90	5	5.55	3	3.33	9	10.0	9	10.0	12	13.33	28	31.11	24	26.6



(a)

Carcinoma Lung Lt.
(a) Before treatment
(b) After treatment

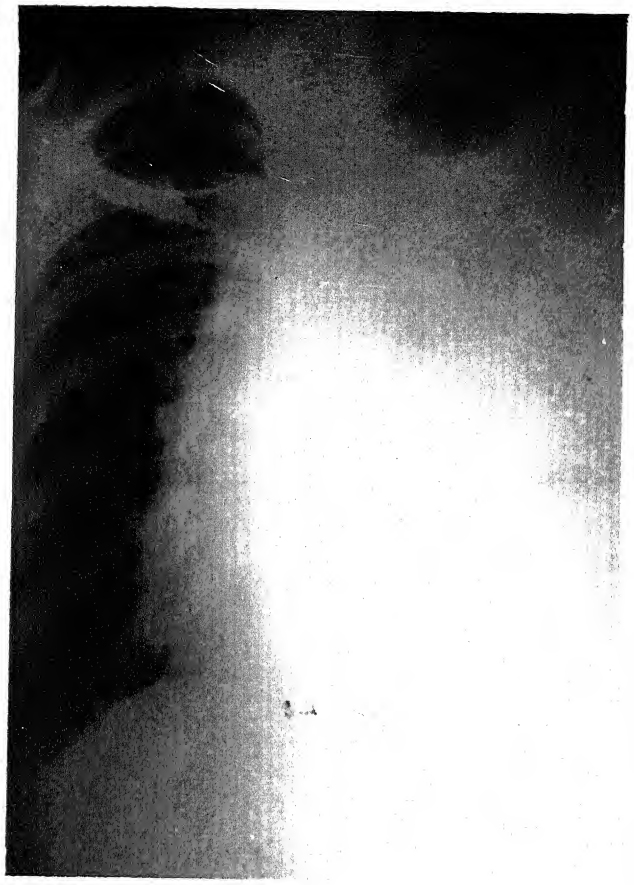


(b)

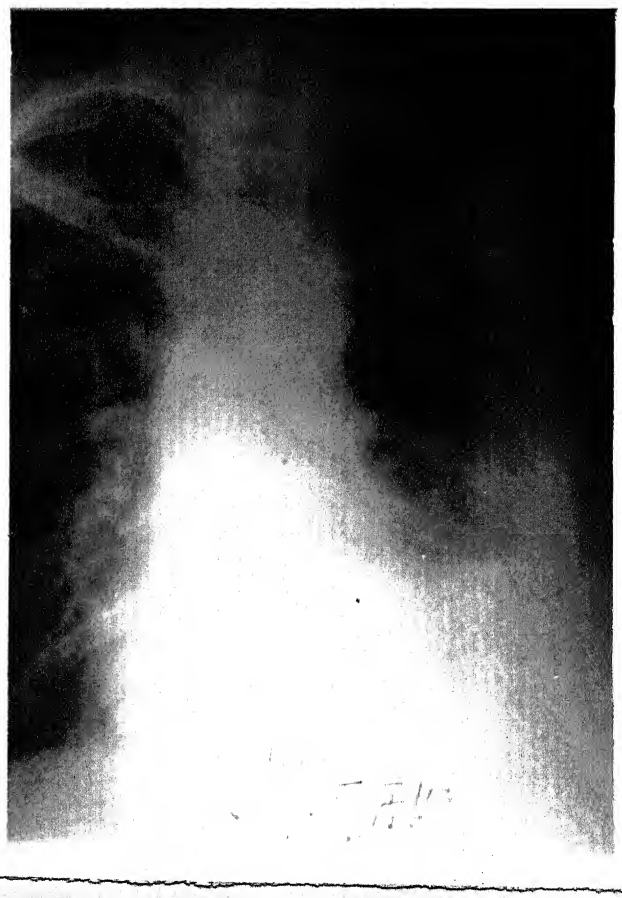
Table No. III

INCEDENCES OF MALIGNANCIES IN MALES & FEMALES :

Malignancy	Type	No. of Patients	MALES Number	%age	FEMALES Number	Percentage
Ca. Breast	Early	11	-	-	11	100.0
	Late	5	1	20.0	4	80.0
Lymphoma	Hodgkin's	5	3	60.0	2	40.0
	N.H.L.	4	3	75.0	1	25.0
	Burkitt's	1	-	-	1	100.0
Leukaemias	ALL	6	4	66.67	2	33.33
	AML	2	1	50.00	1	50.0
	CLL	-	-	-	-	-
	CML	7	4	57.14	3	42.86
G.I.T	Ca Oesophagus	2	2	100.0	-	-
	Ca Stomach	6	4	66.67	2	33.33
	Colorectal Cancer	5	3	60.0	2	40.0
	Ca Pancreas	2	2	100.0	-	-
	Ca Gall Bladder/ Liver	11	7	63.64	4	36.36
Uro-Genital	Overian Cancer	-	-	-	-	-
	Ca testes	2	2	100.0	-	-
	Ca Kidney	-	-	-	-	-
	Ca Prostate	3	3	100.0	-	-
	Ca Bladder	4	4	100.0	-	-
Miscellaneous	Oral Cancers	4	3	75.0	1	25.0
	Ca Head & Neck	6	6	100.0	-	-
	Ca Lungs	4	4	100.0	-	-
	TOTAL	90	56	62.22	34	37.77



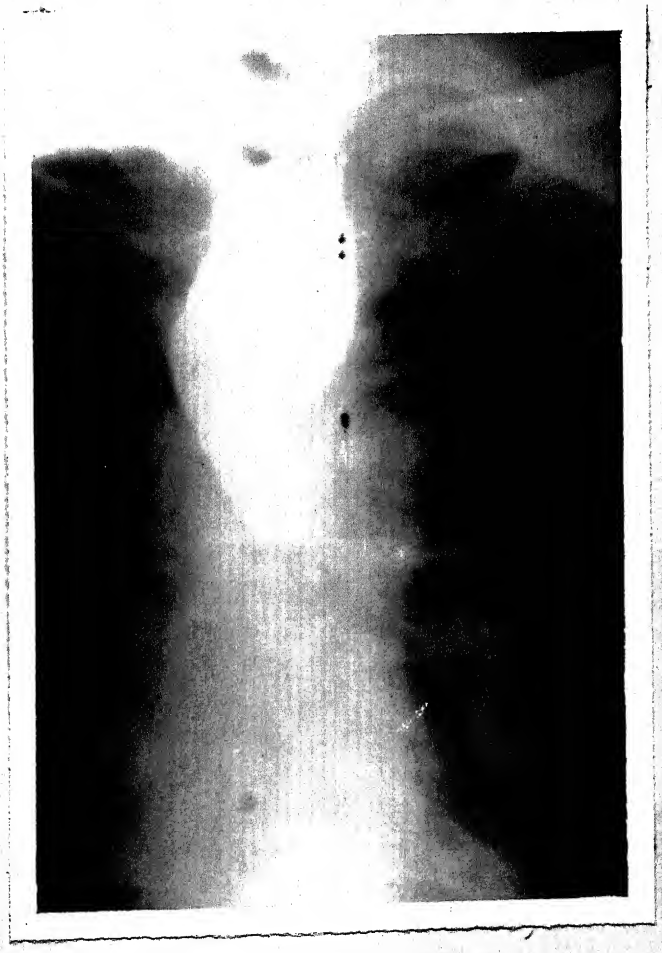
(a)



(b)

Malignant pleural effusion
(a) Before treatment
(b) After treatment

(a)



(b)

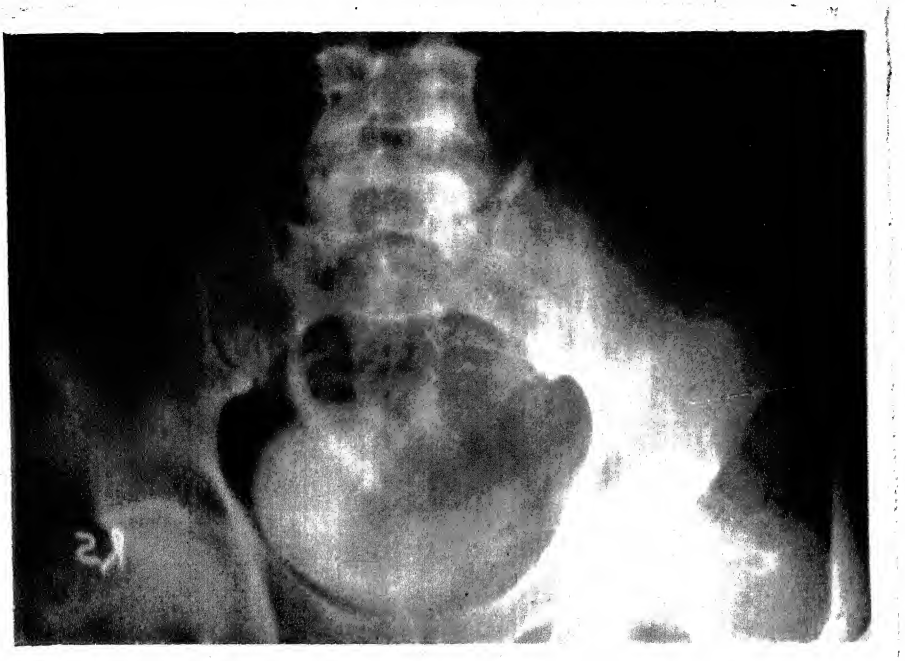
Carcinoma
- oesophagus

(a) Before treatment

(b) After treatment

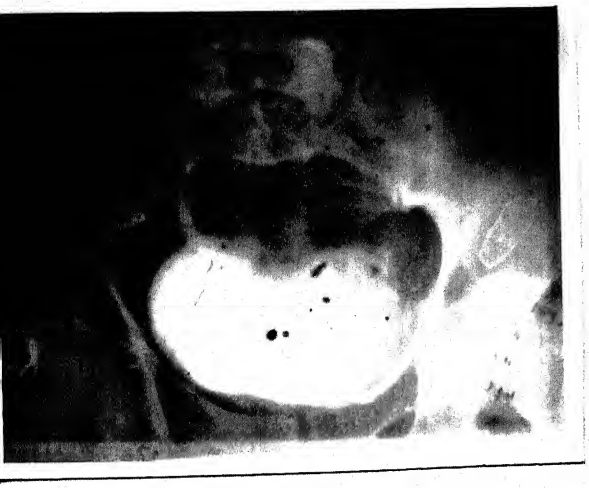
were found to be in equal proportion (18%, 17% respectively). Cancers of uro-genital tract and leukaemias were to the tune of 10% and 11% respectively, while miscellaneous types showed an incidence of 16%. Among individual malignancies early Breast Cancer (12.2%) and carcinoma Gall bladder/Liver (12.2.%) were the Commonest type.

Age pattern for various cancers were studied and results have been listed in Table II. It was observed that early breast cancer (36.3%) was most commonly observed in the age group of 20-30 years, but is rarely seen below 20 years of age, while late Breast cancer (40%) is common among the age group (50-60 yrs.). Lymphoma was of high occurance in the age group of 20-30 years. Most common age group for Hodgkin's Lymphoma (40%) was 10-20 years, while (50%) Non, Hodgkin's Lymphoma was commonly observed between 60-70 years. Acute Lymphocytic Leukaemia was commonest (83.34%) in the age group of 1-10 yrs, while CML was commonly observed (57.16%) in the age group of 20-30 years. Among G.I.T. tumours, Carcinoma stomach, colorectal cancer, carcinoma pancreas were most common (50%, 60%, 100% respectively) in the age group of 50-60 years; while cacinoma Gall Bladder, liver was common (54.55%), in the age group of 60-70 yrs. Cancer of prostate was commonly observed (66.7%) in the age group of 60-70 yrs, while carcinoma urinary bladder was common in age group 50-

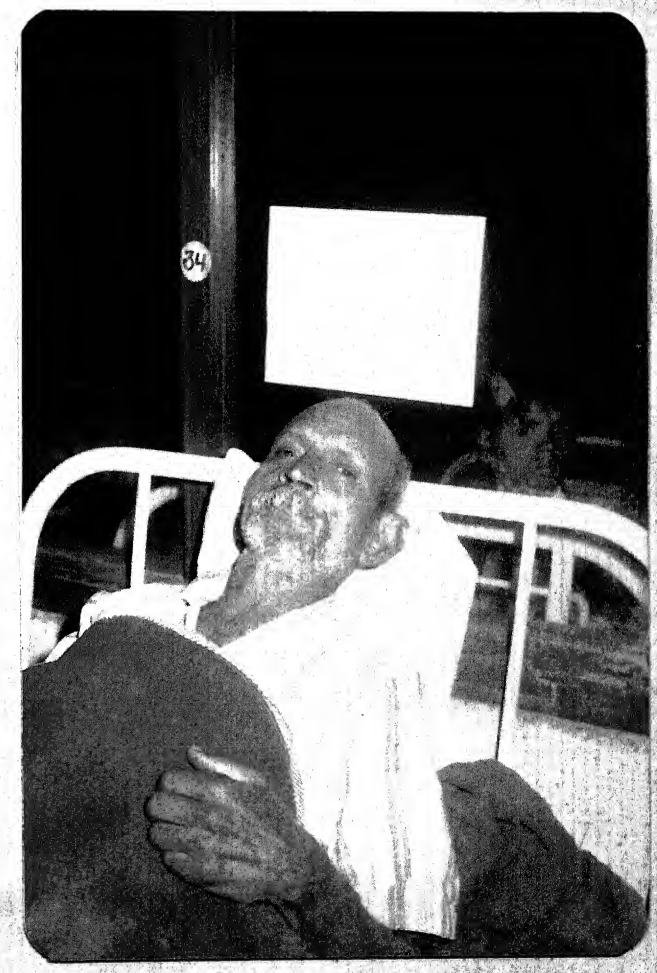


(a)

Carcinoma urinary bladder
(a) Before treatment
(b) After treatment



(b)



70 yrs. Oral cancers were common (75%) in the age group of 50-60 yrs, while carcinoma Head and Neck was common in the older age group (60-70 yrs).

Occurance of cancer in males and females were studied. The results were tabulated in table III. It was seen that Ca.Breast was predominantly seen in female, while Uro-genital carcinoma and cancers of Head & neck & cancer of lungs were most predominantly seen in males (100%). Lymphomas, Leukaemias, cancers of G.I.T. were found to be more common in males than females.

DURATION OF TREATMENT (TABLE IV) :

To evaluate response of treatment following categories of patients were listed on the basis of duration of treatment.

A. Patients who took complete treatment.

B. Patients who took incomplete but adequate treatment.

C. Patients who took incomplete and inadequate treatment:

1. Due to non-compliance.

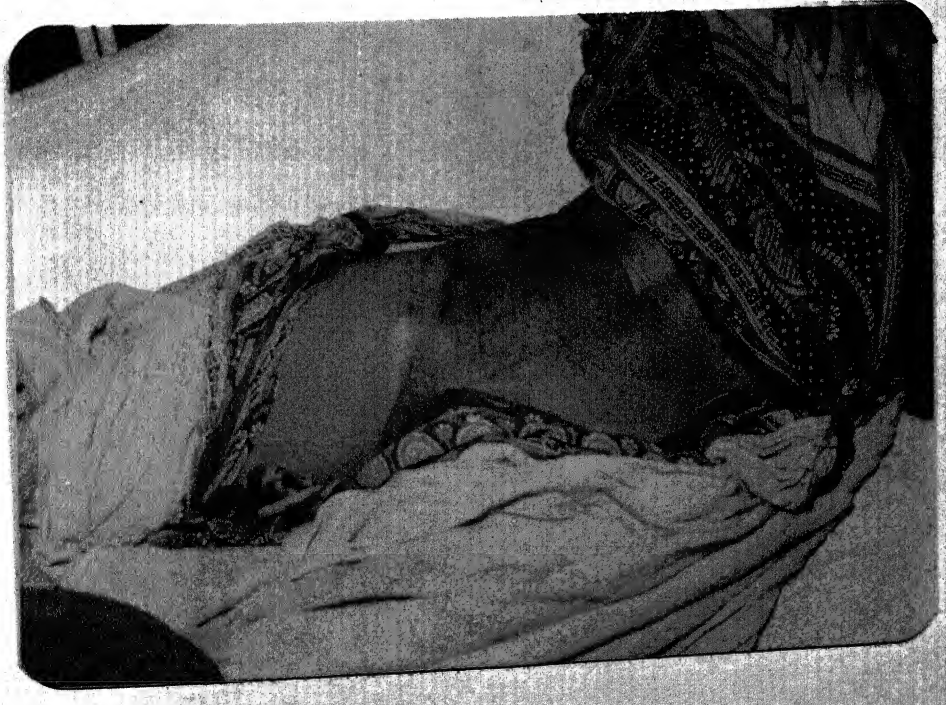
2. Due to toxicity.

Adequate treatment has been taken by patients suffering from breast cancer (94%), lymphomas (80%), G.I.T. malignancies (77%).

Overall 78% patients took complete and adequate treatment

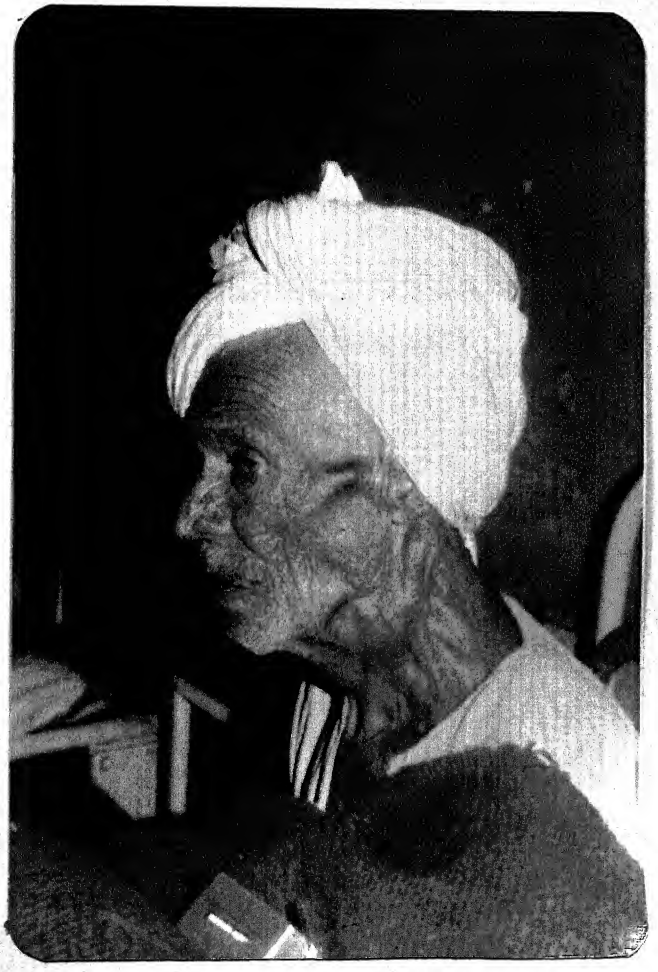
(a)

Hodgkin's Lymphoma
(a) Before treatment
(b) after treatment



(b)

(a)



(b)

Secondaries neck

(a) Before treatment

(b) After treatment.

2. LYMPHOMA (TABLE VI) :

CHEMOTHERAPEUTIC RESPONSE IN LYMPHOMAS :

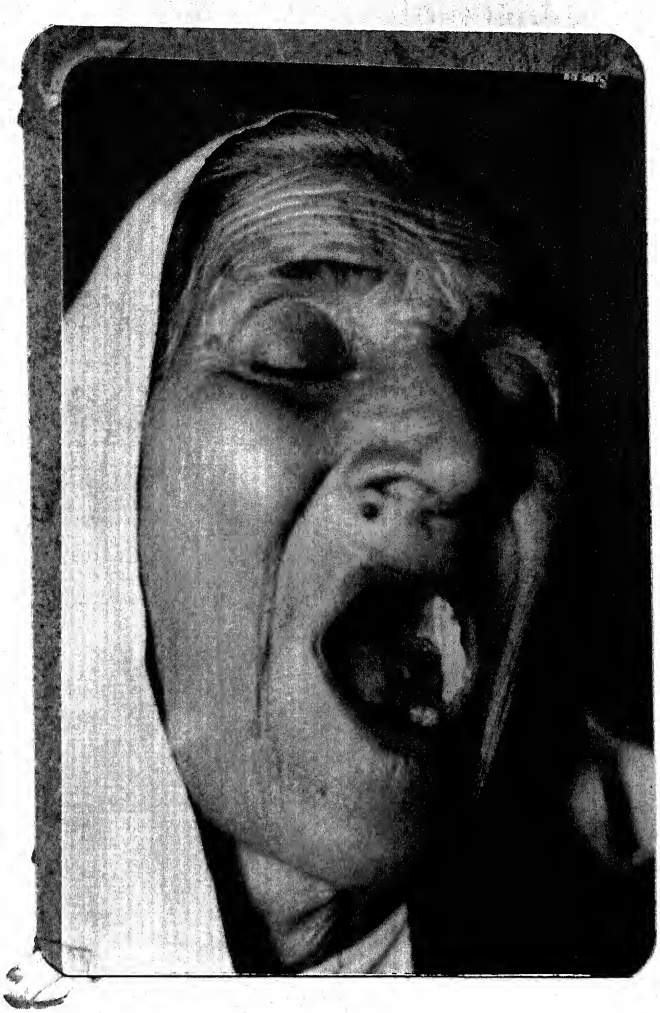
Type of Malignancy	No. of evaluable cases	CR No.	CR %	PR No.	PR %	NR No.	NR %	PD No.	PD %	OR No.	OR %
Hodgkin's Lymphomas	5	3	60	1	20	1	20	-	-	4	80
Non- "	3	1	33.3	1	33.3	1	33.4	-	-	2	66.6
Burkitt's "	1	-	-	-	-	1	100	-	-	-	-

Complete response in Hodgkin's and non-hodgkin's Lymphoma was 60% and 33% respectively while overall response was 80% and 66% respectively.

3. LEUKAEMIAS (TABLE VII)

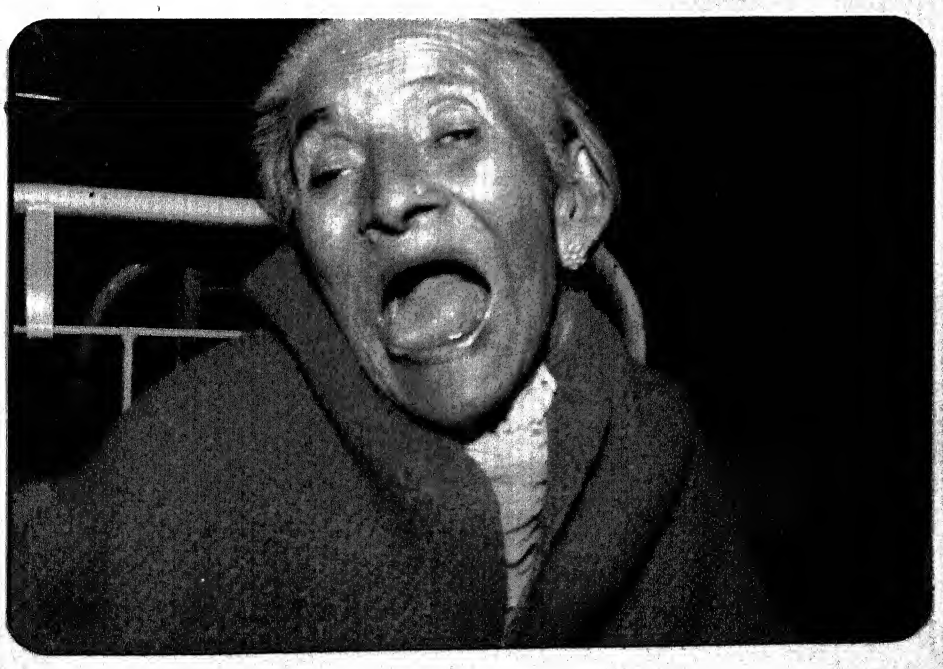
CHEMOTHERAPEUTIC RESPONSE IN LEUKAEMIAS :

Type of malignancy	No. of evaluable cases	CR No.	CR %	PR No.	PR %	NR No.	NR %	PD No.	PD %	OR No.	OR %
ALL	6	2	33.33	-	-	-	-	4	66.67	2	33.33
AML	2	1	50	-	-	1	50	-	-	1	50.0
CLL	-	-	-	-	-	-	-	-	-	-	-
CML	7	2	28.57	1	14.28	2	28.58	2	28.57	3	42.86



(a)

Carcinoma tongue
(a) Before treatment
(b) After treatment.



(b)

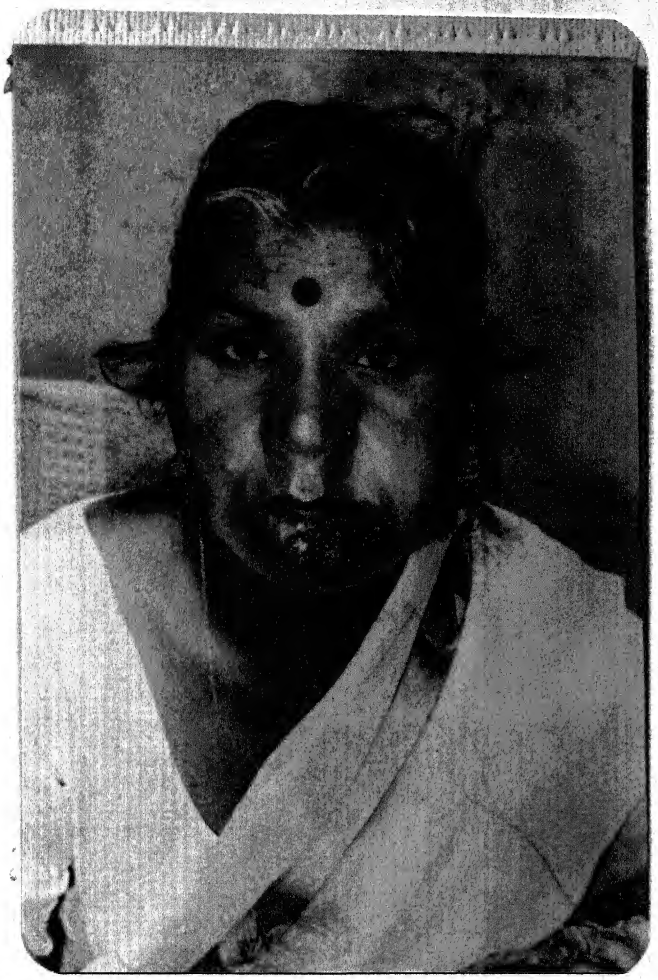
Complete response in Acute Lymphocytic Leukaemia (ALL), Acute Myeloid Leukaemia (AML) Chronic Myeloid Leukaemia (CML) was 33%, 50% 29% respectively. Overall response in ALL, AML, and CML was 33%, 50%, 43% respectively.

4. G.I.T.CARCINOMA (TABLE VIII)

CHEMOTHERAPEUTIC RESPONSE IN G.I.T. :

Type of Malignancy	No. of evaluable cases	CR No.	%	PR No.	%	NR No.	%	PD No.	%	OR No.	%
Ca. Oesophagus	2	1	50	-	-	-	-	1	50.0	1	50.0
Ca. Stomach	6	1	16.6	2	33.3	2	33.4	1	16.7	3	50.0
Colorectal cancer	5	-	-	2	40.0	2	40.0	1	20.0	2	40.0
Ca. Pancreas	2	1	50.0	-	-	1	50.0	-	-	1	50.0
Ca. Gall Bladder & Liver	11	1	9.09	4	36.36	3	27.27	3	27.28	5	45.45

Complete response in Carcinoma Oesophagus and Carcinoma Pancreas was 50%. complete response in Carcinoma Stomach and Carcinoma Gall Bladder and Liver was 16%, 9% respectively. The over all response of chemo-therapy in carcinoma Stomach, colorectal, and Gall bladder & Liver was 50%, 40% & 45%.



(a)

(b)

Carcinoma lip
(a) Before treatment
(b) After treatment.

5. URO-GENITAL CANCER (TABLE IX)

CHEMOTHERAPY RESPONSE IN URO-GENITAL CANCERS

Type of Malignancy	No. of evaluable Cases	CR No.	%	PR No.	%	NR No.	%	PD No.	%	OR No.	%
Ovarian Cander	-	-		-		-		-		-	
Testicular Cancer	2	-		1	50.0	1	50.0	-		1	50.0
Renal Cancer	-	-		-		-		-		-	
Carcinoma Prostate	3	-		2	66.67	1	33.33	-		2	66.67
Carcinoma Bladder	5	-		2	50	2	50	-		2	50

Overall responce in testicular cancer, Carcinoma prostate and carcinoma urinary bladder was 50%, 67%, 50% respectively.

6. MISCELLANEOUS GROUP (TABLE X)

CHEMOTHERAPEUTIC RESPONSE IN MISCELLANEOUS CANCERS

Type of Malginancy	No. of evaluable cases	CR No.	%	PR No.	%	NR No.	%	PD No.	%	OR No.	%
Oral Cancers	4	-		1	25.0	2	50.0	1	25.0	1	25.00
Head & Neck Cancers	6	1	16.66	2	33.33	1	16.66	2	33.34	3	50.0
Lung Cancer	4	-		2	50.0	1	25.0	1	25.0	2	50.0

Overall response in oral cancers, head & neck cancers, and lung cancers was 25%, 50%, and 50% respectively.

TOXICITY

1. Early Toxicity (Table XI)

(a) Nausea & Vomiting, Stomatitis, and Diarrhoea were observed in 29%, 4%, 5% patients respectively.

(b) Fever, hypersensitivity and cystitis were observed in 11%, 2% and 4% case respectively.

Table No. XI

INCIDENCES OF EARLY TOXICITY :

Type of Malign.	Type	No. of Pt.	Signs of Toxicity											
			Nausea & Vomiting		Stomatitis		Diarrhoea		Fever		Hyper Sensivity		Cystiti	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Ca. Breast	Early	11	6	54.54	–	–	2	18.18	1	9.091		9.09	1	9.09
	Late	5	4	80.0	–	–	–	–	–	–	–	–	1	20.0
	Hodgkin's	5	2	40.0	–	–	–	–	–	–	1	20.00	–	–
Lymphoma	NHL	4	1	25.0	–	–	–	–	–	–	–	–	–	–
	Burkitt's	1	–	–	–	–	–	–	–	–	–	–	–	–
	ALL	6	2	33.33	1	16.67	–	–	–	–	–	–	–	–
	AML	2	–	–	–	–	–	–	–	–	–	–	–	–
Leukaemia	CLL	–	–	–	–	–	–	–	–	–	–	–	–	–
	CML	7	---	–	2	28.57	–	–	–	–	–	–	–	–
	Ca Oesophagus	2	–	–	–	–	–	–	–	–	–	–	–	–
	Ca Stomach	6	2	33.33	–	–	–	–	–	–	–	–	–	–
G.I.T.	Colorectal Ca	5	1	20.0	–	–	–	–	–	–	–	–	–	–
	Ca Pancreas	2	–	–	–	–	–	–	–	–	–	–	–	–
	Ca GB, Lever	11	3	27.27	1	9.09	–	–	–	–	–	–	–	–
	Ovarian Ca	–	–	–	–	–	–	–	–	–	–	–	–	–
	Ca. Testis	2	–	–	–	–	–	–	–	–	–	–	–	–
Urogenital	Ca. Kidney	–	–	–	–	–	–	–	–	–	–	–	–	–
	Ca. Prostate	3	2	66.66	–	–	–	–	–	–	–	–	–	–
	Ca. Bladder	4	1	25.00	–	–	–	–	–	–	–	–	-1	25.0
	Oral Cancer	4	1	25.00	–	–	1	25.00	–	–	–	–	–	–
Miscellaneous	Ca. Hd. & Nk.	6	–	–	–	–	–	–	–	–	–	–	–	–
	Ca. Lung	4	–	–	–	–	–	–	–	–	–	–	–	–
	TOTAL	90	26	28.88	4	4.44	3	3.33	1	1.11	2	2.22	4	4.44

Table No. XII

DELAYED TOXICITY

Malignancy	Type	No. of Pt.	SIGNS OF TOXICITY Anemia No.	%	Haemorrhage No.	%	Alopecia No.	%	Leucopenia No.	%
Ca Breast	Early	11	2	18.18	-	-	-	-	3	27.27
	late	5	1	20.00	-	-	-	-	1	20.00
Lymphoma	Hodgkin's	5	1	20.00	-	-	-	-	1	20.00
	Non-Hodgkin's	4	1	25.00	-	-	-	-	1	25.00
	Burkitt's	1	-	-	-	-	-	-	-	-
Leukaemia	ALL	6	-	-	4	66.66	-	-	-	-
	AML	2	-	-	-	-	-	-	-	-
	CLL	-	-	-	-	-	-	-	-	-
	CML	7	-	-	-	-	-	-	-	-
G.I.T.	Ca Oesophagus	2	-	-	-	-	-	-	-	-
	Ca Stomach	6	1	16.67	-	-	-	-	1	16.67
	Colorectal Ca.	5	1	20.00	-	-	-	-	1	20.00
	Ca. Pancreas	2	-	-	-	-	-	-	-	-
	Ca. GB, Liver	11	-	-	-	-	-	-	-	-
Urogenital	Ovarian Cancer	-	-	-	-	-	-	-	-	-
	Ca Testis	2	-	-	-	-	-	-	-	-
	Kidney Caner	-	-	-	-	-	-	-	-	-
	Ca. Prostate	3	-	-	-	-	-	-	-	-
	Ca. Bladder	4	-	-	-	-	-	-	-	-
Miscellaneous	Oral Cancer	4	-	-	1	25.00	-	-	-	-
	Ca. Head & Neck	6	-	-	-	-	-	-	-	-
	Ca. Lungs	4	-	-	-	-	-	-	-	-
	TOTAL	90	7	7.77	5	5.55	-	-	8	8.88

2. Delayed Toxicity (Table XII)

(a) Anaemia, haemorrhage were seen in 8% & 6% cases respectively of our study.

(b) Leucopenia was observed in 8% cases only.

(c) None of our patients suffered from Alopecia.

3. Mortality -

Four patients of acute lymphocytic leukaemia died during treatment. Mortality was very high (67%) in case of ALL. One patient suffering from carcinoma tonge; two patients suffering from Head & Neck Cancer and one patient of Lung Cancer died during the treatment. One patient of Carcinoma Oesophagus and one patient of advanced Colorectal Cancer died during treatment. The overal mortality was 11.11%.

DISCUSSION

DISCUSSION

In the present study, ninty patients suffering from various malignancies were subjected to different chemotherapeutic regimen. Prior to chemotherapy patients were screened and categorised for different types of malignancies and their stages. On examination, it was seen that Breast and gastro-intestinal carcinoma (18% and 29% respectively) were most common types found in our patients. American cancer society (1978) has similarly reported that carcinoma of Breast (in females)26% , carcinoma of gastro-intestinal tract (18%)were dominant types of malignancies. Kemp and Toms, 1978 have also reported that incidences of malignancy in different organs is in the descending order of lung (Males), Breast (females) and G.I.T.

Distribution of cancer in various age group was shown to be more (44%) in age group 40-60. similar reports have been given by William Duncan (1982) maximum at about 45 years and by UICC (1981) (most incidences between 40-45 years of age).

Incidence of prominence of Cancer in different sexes was studied. It was seen that males (62%) had greater tendency to suffer from Cancer, as compared to females (38%). This

observation is supported by reports from American Cancer society and British data (Kemp and Toms, 1978).

It was observed that 70% of patients responded completely to the treatment. High response rates (90-100%) have been reported by De Vita etal, 1970; Goldsmith etal, 1974, using MOPP Regimen. Similar reports were given by Moxley, etal, 1967 and Bonadonna etal, 1975.

In early breast cancer adjuvant chemotherapy after surgery has shown progressive disease in 18% cases in our study while Bonadona etal, 1975; 1976, Showed a relapse of 5.3% after CMF regimen. late stage Breast carcinoma response rate was 22% while other workers, Broader (1974) showed a higher (50-60%) response rate while Cooper (1969) has reported response rate upto 90% with CMFVP regimen. Latest studies with regimens AC, CAF, PM-FAC and FUVAC by Salmon & Jones (1974), Bull, J. (1977). Martimer etal (1985); and Livingstone, etal (1987) respectively have shown 70-80% response. Besides choice of drugs and dosage, response rate also varies with schedule of drugs.

Response rate for Hodgkin's disease was observed in our study to be 80% while other workers have reported response rate of 90-100% using MOPP regimen (De Vita etal, 1970, Goldsmith etal,1974). In other clinical trials 100 % and 90% response with COMP and ABVD regimens respectively have

been shown by Moxley etal, 1967 and Bonadona etal, 1975. Over all response in Non-Hodgkin's Lymphoma was observed to be 67% while Luce etal, 1971 and Bagley etal, 1972; Schein etal, 1975. Mc Kelvey etal, 1975 have shown response upto 60% with BACOP and CHOP regimen. Thus response rate varies according to the combination of drugs.

In the present study over all response in acutre Lymphocytic Leukaemia was 33% while other workers Rodriguez etal, 1973; Jacquillat etal, 1973. Richard Champlin etal 1987 have reported response rate upto 70%. Response to treatment in Leukaemia is to be judged in terms of months or years of survival, without disease. In acute lymphocytic Leukaemia, 5 year leukaemia free survival corresponds to 50% response.

In this study the over all response for acute myeloid leukaemia was observed to be 50%. Similar reports have been documented by Gee etal, 1969.

In Gastric Carcinoma the over all response was 50%, while Kazua etal, 1972; Macdonald etal, 1980; Mortel, C.G., 1976 have shown response rate upto 55%. In Colo-Rectal Carcinoma response rate was 40% while Baker, 1975 reported 30% response. In our study Pancreatic carcinoma has shown a response rate of 50% while Carter and Comis, 1975; Bitran

etal, 1979 and Wiggam, 1978 reported response rates of 30, 45, 50% respectively. Carcinoma Gall Bladder and liver showed 45% response rate while Carter and livingstone, 1970 obtained a response rate of 40-50%.

In our study testicular cancer showed a response rate of 50% while Samuels 1975 reported a response rate of 75%. Response rate of carcinoma Prostate was 66% while Prout, G.R. 1973, has reported a response rate of 80-85%. Jonsson, and Hogberg, B., (1971), observed response rate of 30% by non-hormonal chemotherapeutic agent in resistant cases of Prostate carcinoma. Response rate in bladder carcinoma in our study is 50%, while Carter, S.K. and Wasserman, 1975 observed a response rate of 67%.

response rate of Head and Neck cancer in our study was 50% while Cortes etal, 1972 and Hanham, etal, 1971 reported response rate of 50-60%. Richard and Chambers reported response rate of 85% by using Hydroxyurea as an adjuvant with surgery and radiotherapy. In Lung cancer response rate was 50% in our study while Wasserman, 1975; Bitran, etal 1978, reported a response of 30-55%.

among early toxicity most common symptom observed is nausea and vomiting (29%). In delayed toxicity incidences

of anaemia, haemorrhage, and leucop-enia were 8, 6, 9% respectively and were due to bone marrow depression caused by cyto-toxic drugs.

As time allocated for the present study was too short, long term follow up was not possible and also malignant disease requires at least 3-5 years follow up to judge the efficacy of any regimen. On the basis of our results which are comparable to various reports and are also supported by them, it is justified to recommend chemotherapy for patients suffering from malignancies as a palliative measure in advanced cases or adjunct to surgery and/or radiotherapy for early cancer.

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SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

A prospective study was carried out on ninty patients of cancer who were admitted in wards of M.L.B. Medical College and Hospital, Jhansi. Chemotherapeutic drugs, single or in combination were given according to different types and stages of malignancies and response of treatment was calculated. In our study the various carcinomas encountered were - Carcinoma Breast, Lymphomas, Leukaemias, Gastro-Intestinal Carcinoma, Urogenital carcinoma, Lung Carcinoma, Carcinoma of Head & Neck and Carcinoma of the Oral Cavity. The most common cancer was of gastro-intestinal tract (29%). 40-60 years age group had maximum incidences (49%) of cancer. Most of the malignancies were predominantly observed in male (62%), In our Study 78% patients took adequate treatment. Response rate for early breast cancer was 18% and response rate for late breast cancer was 22%. In our study metastasis was observed to the extent of 20% in breast cancer. response rate in cases of Lymphoma and Leukaemia were 75% and 40% respectively. In G.I.T. cancers and urogenital cancers response rate were 46 and 55% respectively. Response rate in lung and head & neck carcinoma was 50%. Thus the over all response rate varied from 18

to 50% in different malignancies. This variation in response was not only related to combination of drugs, dosage and schedule but also on type and sensitivity of malignancies. Tumours that have not metastasised are subjected to local forms of tretment, surgery or radiotherapy, while the tumour of advanced stage with metastasis or recurrence requires systemic treatment with chemotherapy. Metastatic disease are failure when treated with surgery or radiotherapy, so far, such cases, systemic treatment offers good control.

Chemotherapy can be instituted in any form of malignant disease, localised, disseminated or circulating tumour cells. Now it has been proved that chemotherapy is curative for some forms of cancer while in other cases it is an effective tool to control the tumour and prolongs life of the patient. Chemotherapy has palliative role in advanced cases. Hence chemotherapy is treatment of choice for most of the malignancies.

Cancer chemotherapy is of great potential and needs co-ordination of multi-modality therapy. There has been significant advancement which stresses role of chemotherapy in treatment of cancer over past 30 years. Chemotherapy along with surgery and radiotherapy has proved to be a

boon to cancer patients. Thus our research is paving way for its greater application in all tumours. In future we might have chemotherapeutic agent which would render this dreaded disease 'CANCER' completely curable.

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